## REMARKS

**Claim Amendments.** In addition to claim amendments discussed below, Applicants have replaced SEQ ID NO:7071 with SEQ ID NO:7070 where it appears in the claims. The sequence locations in the CYP1B1 gene for the polymorphisms in SEQ ID NO:7071 and 7070 are identical, and these sequenced differ only with respect to the particular polymorphism at that locus. Thus, SEQ ID NO:7070 is consistent with the prior restriction election.

Claims 1-22, 37-41, and 76-110 are pending in the present case. The Examiner has raised a number of objections and rejections. For clarity, these objection and rejections are listed below in the order in which they will be addressed.

### I. Priority

The Examiner asserts that applicant has not filed certified copies and translations of priority documents in accordance with 35 U.S.C. §119(b).

### II. Objections to the Specification

1. Some drawings allegedly contain sequences not identified by a sequence identifier;
2. The Examiner asserts that there are 743 pages of drawings for only 313 figures described in the text;
3. The Examiner asserts that there are a number of duplicated and missing pages in the specification;
4. The Examiner asserts that there are 743 pages of drawings and notes the application transmittal identified 745 pages of drawings; and
5. The Examiner asserts that there are only 705 pages of sequence listing filed with the application, comprising 4309 sequences, and notes that the new application transmittal indicates 1687 pages of sequence listing.

### III. New Matter

The Examiner asserts that only 4309 sequences were submitted with the application as filed, and that the sequence listing filed on 10/30/2002 comprising 7669 sequences, comprises new matter.

**IV. Claim Rejections.**

1. Claims 1-22, 37-41, and 76-110 are rejected under 35 U.S.C. §101 for allegedly lacking either a specific or substantial asserted utility or a well-established utility.
2. Claims 1-22, 37-41 and 76-110 are rejected under 35 U.S.C. §112, first paragraph as allegedly failing to teach one of skill in the art how to use the claimed invention.
3. Claims 1, 5, 12, and 37-40 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Han, *et al.*, WO 02/30951 ("Han").
4. Claims 1, 12, 37, 39, and 40 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over accession number AC011074 of September 10, 2000.

These objections and rejections are addressed as follows:

**I. Applicants are entitled to the claimed priority date.**

Included herewith are certified copies and translations of Japanese Patent Applications Ser. No. 2000-399,443 filed December 27, 2000, Ser. No. 2001-135,256 filed May 2, 2001, Ser. No. 2001-256,862 filed August 27, 2001, and Ser. No. 2001-395,196 filed December 26, 2001, each of which was filed with the Commissioner of the Japanese Patent Office. Applicants assert that the requirements of 35 U.S.C. §119 are met and the present application is entitled to the claimed priority dates.

**II. Objections to the Specification**

**1.** The Examiner alleges that some drawings contain sequences not identified by a sequence identifier. Applicants note that Figure 313 contains sequences that are not identified by a sequence identifier. Figure 313 is deleted from the specification by the present amendment. The figure is not necessary to the enablement or understanding of the present invention. Deletion of this figure renders this objection moot.

**2.** The Examiner asserts that there are 743 pages of drawings for only 313 figures described in the text. Figures 1-312 consist of 291 drawing sheets, while Figure 313 contains 455 sheets. Thus, the application as filed contained 746 sheets of drawings. With deletion of Figure 313 by the present amendment, there remain 291 sheets of drawings.

**3.** The Examiner asserts that pages 2, 48, 105, 124, and 178 are missing from the specification. Applicants' records show that these allegedly missing pages were present in the application as filed. Applicants provide herewith replacement copies of pages 2, 48, 105, 124, and 178 from the application as filed. The Examiner has further noted duplication of pages 157, 138, 191, 188, and 221. Applicants' records show that these pages were not duplicated in the application as filed. Applicants' request that the Examiner disregard the duplicated sheets. The specification as filed contained 236 pages. The indication of 263 pages on the transmittal document was a typographical error.

**4.** The Examiner asserts that there are 743 pages of drawings and notes the application transmittal identified 745 pages of drawings. A recount shows that 746 sheets of drawings were included with the application as filed. As noted above, Figure 313, comprising 455 pages, is deleted by the present amendment. Applicant requests instruction on any additional correction required in this regard.

**5.** The Examiner asserts that there were only 705 pages of sequence listing filed with the application, comprising 4309 sequences, and notes that the new application transmittal indicated 1687 pages of sequence listing. Applicants' records show that there were 1687 pages of sequence listings in the application as filed. These comprised a first set of sequences numbered from 1 to 3360 on 982 pages, and a second set of sequences, numbered from 1 to 4309 on 705 pages, for a total of 7669 sequences on a total of 1,687 pages of sequence listing. If the set 982 pages of originally filed sequence listing are missing from the USPTO file, Applicants will provide a replacement copy upon request.

Applicants submit that each of the objections above has been addressed and respectfully request that these objections be removed.

**III. New Matter**

The Examiner asserts that only 4309 sequences were submitted with the application as filed, and that the sequence listing filed on 10/30/2002 comprising 7669 sequences comprises new matter. As explained above, Applicants' original application comprised a first set of sequences numbered from 1 to 3360 and a second set of sequences, numbered from 1 to 4309, for a total of 7669 sequences. In the sequence listing filed on 10/30/2002, the sequence listings were combined and renumbered from 1-7669, as shown in Table 1. No sequences were added and the renumbering does not add new matter to the specification.

The Examiner also points to the missing pages 105 and 124 and asserts that because pages 105 and 124 and the sequences they contain are missing from the specification, the addition of the complete sequence listing of 7669 sequences contains new matter. However, as discussed above, pages 105 and 124 were present in the application as filed. Further, the complete set of 7669 sequences was also present in the application as filed, in the two sequence listings described above. As such, the application as filed comprised each and every one of the 7669 sequences submitted on 10/30/2002, and this sequence listing thus does not contain new matter. Applicants respectfully request that this objection be removed.

## IV. Claim Rejections.

### 1. Claims 1-22, 37-41 and 76-110 have specific and credible utility.

Claims 1-22, 37-41, and 76-110 stand rejected under 35 U.S.C. §101 for allegedly lacking either a specific or substantial asserted utility or a well-established utility. In response, Applicants respectfully assert that the claimed invention is supported by patentable utilities. Applicants specifically disclose and claim methods comprising detecting the recited polymorphisms associated with the CYP1B1 gene region. As noted by the Examiner, the CYP1B1 gene is responsible for about 75% of Phase I dependent drug metabolism (Office Action page 13, citing Sundberg, *et al.*). Sundberg demonstrates the utility of detection methods that permit detection of particular allelic variations associated with the CYP1B1 gene (see, *e.g.*, Sundberg page 99, cols 1-2). As such, methods comprising detection of variants of the CYP1B1 gene have utilities that are well established in the art. Because the detection of variants of CYP1B1 genes has such established utilities, a skilled artisan would recognize that the claimed invention also has utilities that are well established in the art. For example, a skilled artisan would appreciate that the claimed methods for detection of the particular variants recited can be used to detect these particular variants of the CYP1B1 gene in a subject or sample.

The Examiner asserts that a large quantity of experimentation would be required to determine the effect of the claimed polymorphisms, and to determine whether the effect could be used to design a drug or treatment protocol, or determine a prognosis (Office Action, page 13-14). For business reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the original or similar claims in the future, the claims herein have been amended to remove reference to particular diagnostic, prognostic and therapeutic applications.

As discussed above, in view of the well-established utilities of the CYP1B1 gene, a skilled artisan would appreciate the utility of the claimed methods comprising detection of the specified polymorphisms in SEQ ID Nos: 7063, 7064, 7070, 7073, and 7074. Applicants submit that the invention as claimed has specific, well established utility, and respectfully request that these rejections be removed.

2. **Claims 1-22, 37-41 and 76-110 are enabled.** Claims 1-22, 37-41 and 76-110 are rejected under 35 U.S.C. §112, first paragraph as allegedly failing to teach one of skill in the art how to use the claimed invention. The claims as amended provide methods comprising detection of the specified polymorphisms in SEQ ID Nos: 7063, 7064, 7070, 7073, and 7074. Further, the specification provides specific guidance regarding assay methods that are particularly useful in practicing the methods of the invention. As the Examiner has pointed out, the level of skill in the art is high (Office Action, page 15). Applicants have provided description of a number of nucleic acid analysis methods suitable for use in the claimed methods (see, *e.g.*, p176, line 17 through p 185, line 11), and submit that the specification provides ample teaching to allow a skilled artisan to use the claimed invention. Applicants respectfully request that these rejections be withdrawn.

3. **Claims 1, 5, 12, and 37-40 are not anticipated by Han.** Claims 1, 5, 12, and 37-40 stand rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Han. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. MPEP 2131, citing *Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d. 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).* Han does not set forth each and every element of Claims 1, 5, 12, and 37-40. Claims 1, 5, 12, and 37-41 are directed to methods comprising detection of particular polymorphisms in SEQ ID NOS: 7063, 7064, 7070, 7073, and 7074. Particularly, these claims are directed toward detection of polymorphisms at specific sites within these sequences: in SEQ ID NO: 7063, said polymorphism is designated by an r, wherein r is an a or a g, wherein in SEQ ID NO: 7064 said polymorphism is designated by an s, wherein in SEQ ID NO: 7070, said polymorphism is designated by an n, wherein n is t or a deletion, wherein in SEQ ID NO 7073 said polymorphism is designated by an n, wherein said n is an a or a deletion, and wherein in SEQ ID NO: 7074 said polymorphism is designated by an n, wherein said n is an a or a deletion. Han discloses a wild-type nucleic acid sequence of CYP1B1 and a number of specifically identified polymorphisms in the gene. However, Han does not disclose polymorphisms at the

identified sites in SEQ ID NOS: 7063, 7064, 7070, 7073, and 7074. Further, Han does not disclose methods comprising detecting these particular polymorphisms. As Han does not disclose the particular polymorphisms recited in the instant claims or methods comprising detecting them, Han cannot anticipate these claims. For this reason, Applicants' respectfully request that these rejections be removed.

**4. Claims 1, 12, 37, 39, and 40 are patentable over accession number AC011074.** Claims 1, 12, 37, 39, and 40 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over accession number AC011074 of September 10, 2000. The Examiner asserts that the claims of the instant application are drawn to detecting any polymorphism in the recited sequences. For business reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the original or similar claims in the future, the claims herein have been amended to recite methods comprising detection of polymorphisms in SEQ ID NOS: 7063, 7064, 7070, 7073, and 7074, wherein in SEQ ID NO: 7063, said polymorphism is designated by an r, wherein r is a g or an a, wherein in SEQ ID NO: 7064 said polymorphism is designated by an s, wherein in SEQ ID NO: 7070, said polymorphism is designated by an n, wherein n is a t or a deletion, wherein in SEQ ID NO 7073 said polymorphism is designated by an n, wherein said n is an a or a deletion, and wherein in SEQ ID NO: 7074 said polymorphism is designated by an n, wherein said n is an a or a deletion.

As amended, the claims herein recite methods comprising detection of specific polymorphisms. Accession number AC011074 does not teach or make obvious these specifically identified polymorphisms, or the methods of the instant claims. As such, the present claims are not obvious in view of accession No. AC011074 and Applicants respectfully request that these rejections be removed.

**CONCLUSION**

For the reasons set forth above, it is respectfully submitted that all objections and rejections have been addressed and should be removed, and Applicants' claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608) 218-6900.

Dated: 6/28/2005

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There are several types of DNA sequence variations in the human genome. These variations include insertions, deletions and copy number differences of repeated sequences. These differences in the genetic code are called genetic polymorphisms. The most common DNA sequence variations in the human genome are single base pair substitutions. These are generally referred to as single nucleotide polymorphisms (SNPs) when the variant allele has a population frequency of at least 1%. SNPs may be classified by where they appear in the genome. For example, a single nucleotide polymorphism may be classified as a coding SNP (cSNP) when it is in a region encoding a protein, or genome SNP (gSNP) when it is detected anywhere in a genome, without reference to whether it is in a coding region. Coding SNPs include silent SNPs (sSNP), and SNPs that may be in regions associated with coding sequences, such as regulatory regions or elements (*e.g.*, regulatory SNPs, or rSNPs) and introns (*e.g.*, intron SNPs, or iSNPs).

SNPs are particularly useful in studying the relationship between DNA sequence variations and human diseases, conditions and drug responses because SNPs are stable in populations, occur frequently, and have lower mutation rates than other genome variations such as repeating sequences. In addition, methods for detecting SNPs are more amenable to being automated and used for large-scale studies than methods for detecting other, less common DNA sequence variations.

Single nucleotide polymorphisms are useful as polymorphism markers for discovering genes that cause or exacerbate certain diseases. This is directly related in clinical medicine to diagnosing the risk for a disease and determining the proper pharmaceutical treatment. There is currently a worldwide effort going on to develop drugs based on the target genes that cause diseases. Individual patients also react differently when a drug is administered. In some patients, a drug may have a significant effect, in others a lesser effect and in still others no effect at all. In other words, there is a major difference in patient reactions to the same drug. Patients may also metabolize drugs at different rates. In addition to differences in therapeutic reactions among patients to drugs, there is also the possibility of strong and even fatal side effects due to genetically linked differences in, *e.g.*, drug metabolism, drug transport or drug receptor

The invention further features predictive medicines, which are based, at least in part, on determination of the identity of DME polymorphic regions that are associated with particular drug responses. For example, information obtained using the diagnostic assays described herein (alone or in conjunction with information on another genetic defect, which contributes to the same disease) is useful for determining if a test subject has an allele of a polymorphic region that is associated with a particular drug response. Knowledge of the DME profile in an individual (the DME genetic profile), alone or in conjunction with information on other genetic defects contributing to the same disease (the genetic profile of the particular disease) allows customization of therapy for a particular disease to the individual's genetic profile, the goal of "pharmacogenomics." For example, an individual's DME genetic profile can enable a doctor: 1) to more effectively prescribe a drug that will address the molecular basis of the disease or condition; and 2) to better determine the appropriate dosage of a particular drug.

The ability to target populations expected to show the highest clinical benefit, based on the DME genetic profile, allows: 1) the repositioning of marketed drugs with disappointing market results; 2) the rescue of drug candidates whose clinical development has been discontinued as a result of safety or efficacy limitations, which are patient subgroup-specific; and 3) an accelerated and less costly development for drug candidates and more optimal drug labeling (e.g. since the use of DMEs as markers is useful for optimizing effective dose).

## DETAILED DESCRIPTION OF THE INVENTION

Examples of genetic polymorphism data related to a DME, and useful in the detection, evaluation method and screening methods of the present invention are shown in Table 1.

**Table 1**

| GENE | NO | LOCATION | SEQ. | SEQ ID NO. |
|---|---|---|---|---|
| ALDH1L1 | 106 | 3'flanking+145 | gagcgacaggaggaaatggg C/T gtgggtcatctcaggcccca | 3344 |
| ALDH1L1 | 107 | 3'flanking+239 | tgggaaacaggtgggaagac G/A gggattgagctgggtgagcc | 3345 |
| ALDH1L1 | 108 | 3'flanking+288 | ggcagcagctcagactccct C/T agcagatgaggccgggccct | 3346 |
| ALDH1L1 | 109 | 3'flanking+1513 | agggtcggctcagaccccgg A/C gtgctcctggcatgtccagc | 3347 |
| ALDH1L1 | 110 | 3'flanking+1707 | cggtgggacttgccctagca C/T gtgccacttatcccagaaca | 3348 |
| ALDH1L1 | 111 | 3'flanking+1709 | gtgggacttgccctagcacg C/T gccacttatcccagaacaga | 3349 |
| ALDH1L1 | 112 | 3'flanking+1745 | acagatgagtccatgtcaac C/T gcttcctgagttcccttgt | 3350 |
| ALDH1L1 | 113 | 3'flanking+1843 | ctgcctctcagcccacagcc G/A ggccgctcacactcctccca | 3351 |
| CYP3A4 | 1 | intron2+(754-763) | cacaaaatgagtttgtgggg (T)9-11 acacaaaggcggaatcacat | 3352 |
| CYP3A4 | 2 | intron7+258 | acccactaatcaactttctgc C/T tctatggattgcctattct | 3353 |
| CYP3A4 | 3 | intron7+894 | tgctgatctcactgctgtag C/T ggtgctccttatgcatagac | 3354 |
| CYP3A4 | 4 | exon9+(32-33) | ttccttcagctgatgattga (A) ctctcagaattcaaaagaaa | 3355 |
| CYP3A4 | 4 | exon9+(32-33) | ttccttcagctgatgattga ctctcagaattcaaaagaaa | 3356 |
| CYP3A4 | 5 | intron10+12 | cccaataaggtgagtggatg G/A tacatggagaaggagggagg | 3357 |
| CYP3A4 | 6 | intron10+459 | agacatgtgacttttttttt T/Δ gaaaggtaacaatcacttic | 3358 |
| CYP3A4 | 7 | intron10+608 | agccgtctcgaatgtctccc C/T acttcataactcctccacac | 3359 |
| CYP3A4 | 8 | intron12+2467 | ttttttgcccattactccat A/G gagatcagaatatcactctg | 3360 |

## Table 1

| GENE | NO | LOCATION | SEQ. | SEQ ID NO. |
|---|---|---|---|---|
| ABCC9 | 7 | intron 4 + 1022 | tactgtggaatttttcttgc A/C acagagatatgtatttttca | 4573 |
| ABCC9 | 8 | intron 5 - 1217 | cagtggtagatgtgtttttct A/G ttgccatcatctacaaatat | 4574 |
| ABCC9 | 9 | intron 6 + (100-106) | tatgagttgttcaaataggc (T)8-9 cagagaattgaatgctttct | 4575 |
| ABCC9 | 10 | intron 6 + 1347 | tcagtcgtattcctactaaa A/Δ caaaattttgtaagttatgt | 4576 |
| ABCC9 | 11 | intron 6 + 1618 | ctttttatttgctgcttacc G/A ttttactaaggttggatata | 4577 |
| ABCC9 | 12 | intron 6 + 1835 | cttttaataaatgcaaactg C/T acacctggtctataaaaaga | 4578 |
| ABCC9 | 13 | intron 7 + 407 | cctatagaatttttctttttc T/G tttttctcaaaaaaattaaa | 4579 |
| ABCC9 | 14 | intron 7 + 423 | tttctttttttctcaaaaaaa C/T taaatgtttgttatttattt | 4580 |
| ABCC9 | 15 | intron 8 + 743 | ttctgtagatgaagcttaag A/T gctagatcttatttgaaaaa | 4581 |
| ABCC9 | 16 | intron 8 + 850 | tttttaacttattgtttgcc T/G tttcatttttttaatagaaaa | 4582 |
| ABCC9 | 17 | intron 9 + 585 | cgaatttgctgcttttagag A/T aatctttgcaaataataaaa | 4583 |
| ABCC9 | 18 | intron 9 + 1394 | atttttcttcttgtaagtat G/C agtgatagagctgactgcag | 4584 |
| ABCC9 | 19 | intron 12 + 1167 | atttgtaagacttttaaaat G/A agataattgtgctggtgtct | 4585 |
| ABCC9 | 20 | intron 12 + 1195 | tgtgctggtgtctatatctt A/G ctgagaaaactagaatttat | 4586 |
| ABCC9 | 21 | intron 12 + 2123 | ataagtgctctcccagtgtt G/A attggacttagagcattttc | 4587 |
| ABCC9 | 22 | intron 12 + (2653-2656) | caaaacagaataatgaaaag TAAC/Δ tattatctaaaataataaaa | 4588 |
| ABCC9 | 23 | intron 13 + (3043-3044) | aacatactctcctcctctct (CTCTTT) aagtcaaaatatattagtat | 4589 |
| ABCC9 | 23 | intron 13 + (3043-3044) | aacatactctcctcctctct (CT) aagtcaaaatatattagtat | 4590 |
| ABCC9 | 23 | intron 13 + (3043-3044) | aacatactctcctcctctct aagtcaaaatatattagtat | 4591 |
| ABCC9 | 24 | intron 14 + 85 | ttctgtgaaagtgtcccaaa T/A tgtgcctttaaattgttttt | 4592 |
| ABCC9 | 25 | intron 14 + 275 | agtgtcacatgtatttttttc T/C ggtattcctatgtttatcaa | 4593 |
| ABCC9 | 26 | intron 14 + 453 | ctcatttcaaacttggctat T/C tggactctccccaggcattg | 4594 |
| ABCC9 | 27 | intron 14 + 3709 | atcccctagtgatgtacact G/A agcttgcctccatctttcct | 4595 |
| ABCC9 | 28 | intron 14 + 3813 | ctgatttatatattagctga C/T tttccaagttcagacatcta | 4596 |
| ABCC9 | 29 | intron 14 + 4000 | ttcttttacttcaatgtagc A/Δ ccaaatcagaaggtgacatt | 4597 |
| ABCC9 | 30 | intron 16 + 1466 | atcccactggatttaattac A/C ttgtgtagcttgtacaacca | 4598 |
| ABCC9 | 31 | intron 16 + 5357 | attttggaagagaaattata T/G aaccttccacaactgaattt | 4599 |
| ABCC9 | 32 | intron 17 + 1368 | aatcctggtgtttttttttt T/Δ ctttttcatttttcagtagg | 4600 |
| ABCC9 | 33 | intron 20 + 98 | aagtaactcaaggaaagatg G/A tttaacttgtgaaatcgtaa | 4601 |
| ABCC9 | 34 | intron 22 + 28 | ctcatagttcagaagagttc A/C gagcccaattcagaagagtt | 4602 |
| ABCC9 | 35 | intron 22 + 194 | tgaacctataaaattctaat G/Δ ccatctttggatgaggtgca | 4603 |
| ABCC9 | 36 | intron 22 + 1370 | ccagggacaaaagaagatga C/T gtaaacttaaggattgggac | 4604 |
| ABCC9 | 37 | intron 22 + 1487 | agcaagccaggaagaaagtc C/G attaagttgtatttagaaat | 4605 |
| ABCC9 | 38 | intron 23 + (455-462) | atagccatgaaggataagaa AATTAGAA/Δ tgccatttgttatgtttc | 4606 |
| ABCC9 | 39 | intron 24 + (460-465) | aactctttctcttcatctgc TTTAAAA/TTTTAA gcaagccttgaagga | 4607 |
| ABCC9 | 40 | intron 24 + 595 | gcatgcaaaataatgaagaa A/G acaatcttgtctgacattga | 4608 |
| ABCC9 | 41 | intron 28 - 926 | aaatatttcagaatttgggg G/A tgtagagcatttgccgtcat | 4609 |
| ABCC9 | 42 | intron 29 + 2692 | cttgtaagtctttttttttt T/Δ aaagtaatgaaaatttctaa | 4610 |
| ABCC9 | 43 | intron 29 + 5464 | agacaacactgctttttgt G/A tgttcacaattcaacgacag | 4611 |
| ABCC9 | 44 | intron 29 - 1830 | aactggctgaaaggaaaaaa A/T tcatattgctgtaaatattt | 4612 |
| ABCC9 | 45 | intron 31 + 102 | tgcttttgctttccacttca G/A tatccagaaaactctctcat | 4613 |
| ABCC9 | 46 | intron 33 + 877 | aacatggaactatagtaaat A/G tagttttttggggttcaga | 4614 |
| ABCC9 | 47 | intron 36 + 1281 | aatttacacttttttttttt T/Δ gcaggagaatattttgcaaa | 4615 |
| ABCC9 | 48 | 3'flanking + 197 | aatggagctcatgcatgtgt T/G ttcaaatatatacatgcaaa | 4616 |
| ABCD1 | 1 | (5' flanking region -1772 | agtcccagggctagggcaca G/A gcaccctcctgcctaactcg | 4617 |
| ABCD1 | 2 | (5' untranslated region - | acaatccttccagccacctg C/T ctcaactgctgccccaggca | 4618 |
| ABCD1 | 3 | (intron 1 906) | gggcacaatggcatccatcc C/T ccgaaggcctgtgtgtgctc | 4619 |
| ABCD1 | 4 | (intron 1 2924) | gagacctggccccacccaat C/T gtaacctctggctctcggcc | 4620 |
| ABCD1 | 5 | (intron 1 3056) | aagcctctctgtgtctgtca C/T cccccgcaggtggagctggc | 4621 |
| ABCD1 | 6 | (intron 2 2972) | agaagtttcccttgctttcc G/A tcaagcttggctctgctcga | 4622 |
| ABCD1 | 7 | (intron 2 3258) | gcgagacagcacctgcagcc G/A cttcgctccatggctgccat | 4623 |
| ABCD1 | 8 | (intron 2 4612) | ggtccttcacaggacattcc C/T accacttcagccacacccca | 4624 |
| ABCD1 | 9 | (intron 5 2748) | aatggcctgcgtgctggcct C/T gggcattgggagcctctcaa | 4625 |
| ABCD1 | 10 | (intron 6 212) | atctgtgtggggtgtgtgca C/T gggcggcgatgtgagcgtgt | 4626 |
| ABCD1 | 11 | (intron 5 2835) | ggcgtcagcggctgttgccc C/Δ tgcaggtggaggaaggcatg | 4627 |
| ABCD3 | 1 | (5' flanking region -2834 | acatccctttcttgcctggc A/G gatttgaactctttgagtca | 4628 |
| ABCD3 | 2 | (5' flanking region -2118 | tacagaatcacctttgtcaa G/A ccttaagcctttattgaaag | 4629 |
| ABCD3 | 3 | (5' untranslated region -4 | gtagccgccgccgccgccgc C/T gccgcgtcccctcgccggct | 4630 |
| ABCD3 | 4 | (intron 1 -6763) | atactttgccatttgagata T/C cagtttggagttgatagctg | 4631 |
| ABCD3 | 5 | (intron 2 731) | ctttggacctatactagttt C/T cttaggcattgtgcttagaa | 4632 |
| ABCD3 | 6 | (intron 2 3551) | accacagtggtctttttttt A/G tatttaaaaaaattattggg | 4633 |
| ABCD3 | 7 | (intron 2 5936) | cagaactcacttccttattc A/G gtttttagataacattgttt | 4634 |
| ABCD3 | 8 | (intron 2 6083) | tggttctttaattttatgat A/G tgtttgttatagctatctta | 4635 |
| ABCD3 | 9 | (intron 3 614) | tctcttgtttctgaagtatt A/T tttcattttattttatgtga | 4636 |
| ABCD3 | 10 | (intron 3 651) | gtgaaatgctagggtactgc C/T atacagctaccctaaatggt | 4637 |
| ABCD3 | 11 | (intron 4 395) | aaagcatttcaaagaatcac G/A ttgagcatgtttattagaag | 4638 |
| ABCD3 | 12 | (exon 7 555) | gacaacagaatagctaatcc A/G gaccagctgcttacacaaga | 4639 |
| ABCD3 | 13 | (intron 7 124) | aaatatttaatgctttttata A/G gaaaattagagttgttgtaa | 4640 |
| ABCD3 | 14 | (intron 7 838) | ggtcacagttgacctagata T/C acagttttgagacaaaagaa | 4641 |
| ABCD3 | 15 | (intron 8 1150) | aatcttgaatacttactagc A/C catatattgtgctagatagt | 4642 |

is herein incorporated by reference). This assay is based on the observation that when single strands of DNA fold on themselves, they assume higher order structures that are highly individual to the precise sequence of the DNA molecule. These secondary structures involve partially duplexed regions of DNA such that single stranded regions are juxtaposed with double stranded DNA hairpins. The CLEAVASE I enzyme, is a structure-specific, thermostable nuclease that recognizes and cleaves the junctions between these single-stranded and double-stranded regions.

The region of interest is first isolated, for example, using PCR. In preferred embodiments, one or both strands are labeled. Then, DNA strands are separated by heating. Next, the reactions are cooled to allow intrastrand secondary structure to form. The PCR products are then treated with the CLEAVASE I enzyme to generate a series of fragments that are unique to a given SNP or mutation. The CLEAVASE enzyme treated PCR products are separated and detected (*e.g.*, by denaturing gel electrophoresis) and visualized (*e.g.*, by autoradiography, fluorescence imaging or staining). The length of the fragments is compared to molecular weight markers and fragments generated from wild-type and mutant controls.

### 4. Hybridization Assays

In preferred embodiments of the present invention, variant sequences are detected a hybridization assay. In a hybridization assay, the presence of absence of a given SNP or mutation is determined based on the ability of the DNA from the sample to hybridize to a complementary DNA molecule (*e.g.*, a oligonucleotide probe). A variety of hybridization assays using a variety of technologies for hybridization and detection are available. A description of a selection of assays is provided below.

#### a. Direct Detection of Hybridization

In some embodiments, hybridization of a probe to the sequence of interest (*e.g.*, a SNP or mutation) is detected directly by visualizing a bound probe (*e.g.*, a Northern or Southern assay; *See e.g.*, Ausabel *et al.* (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY [1991]). In a these assays, genomic DNA (Southern) or RNA

**Amendments to the Drawings.**

Please delete Figure 313.